

Classification of Ocular Atopic/Allergic Disorders and Conditions: an Unsolved Problem

Margarita Calonge, M.D.

Ocular Immunology Unit, Institute of Ophthalmobiology (IOBA), University of Valladolid, Valladolid, Spain

ABSTRACT.

Purpose: To review the different classifications of ocular allergic diseases and to define the most suitable one according to the current understanding of the pathophysiology and clinical course of these disorders.

Methods: Review of the major published ocular allergy classifications.

Results: Based on past and present classifications, the author proposes the following classification: 1. allergic conjunctivitis (acute and chronic); 2. giant papillary conjunctivitis; 3. vernal keratoconjunctivitis; and 4. atopic keratoconjunctivitis. In addition, use of the term "allergic conjunctivitis" as a synonym for all ocular allergic disease is discouraged.

Conclusion: The proposed classification for ocular allergic disorders intends to unify the present criteria and to serve as an initial forum of discussion. This should enhance a common understanding among and between ophthalmologists and other allergy specialists. Constructive criticism of this classification system is required for further improvement.

Key words: allergic conjunctivitis – atopic keratoconjunctivitis – drug allergy – giant papillary conjunctivitis – ocular allergies – ocular atopy – seasonal conjunctivitis – perennial conjunctivitis – vernal keratoconjunctivitis

Acta Ophthalmol. Scand. 1999; 77: 10–13

Copyright © Acta Ophthalmol Scand 1999. ISSN 1395-3907

Introduction

Allergic ocular problems represent a broad spectrum of ocular diseases that occur frequently in clinical practice. A type I immediate hypersensitivity mechanism has been proven for the various allergic eye disorders. However, other mechanisms such as late phase type I reactions, non-IgE-mediated activation of mast cells, type IV hypersensitivity (delayed T cell-mediated), and nonspecific conjunctival hypersensitivity as well as genetic, neuronal, hormonal and climatic factors) have also been implicated. This variety of etiologic implications gives a more complex immunological basis and a chronic inflammatory component to these disorders (1–8). Unfortunately, it is still not well understood how these fac-

tors orchestrate to explain the different clinical pictures. Accordingly, classification of the different allergic ocular diseases remains controversial, and there is no consensus among the different experts in this field. The consequences of this lack of a common language are that the prevalence and incidence of the various clinical entities is not well established, the diagnostic procedures are not well standardized, and therefore therapy is often empirical. This is of paramount importance because while some forms of atopic ocular disorders have no visual consequences, others can result in corneal involvement and a subsequent permanent reduction in vision.

This report aims to establish a classification system for the diverse ocular allergic disorders that will be commonly

accepted worldwide. This will allow all allergic ocular events to be properly classified. To achieve this goal, a review of the major published classification systems has been made and a tentative classification is offered based on the current popular opinion. This should facilitate the sharing of a common scientific language and therefore, the unification of research, clinical and therapeutic criteria.

Materials and Methods

A selection of the main classifications over the past 20 years was made through Medline (PubMed, National Library of Medicine, Bethesda, MD, USA). In addition, past and current books and manuscripts available to the author on this issue were reviewed.

Results and Discussion

Review of published classifications for ocular allergies

After reviewing the past and present literature in this field, it becomes clear that the current classifications are confusing, at best. Inconsistent terminology appears to be at the root of the confusion. The following is an attempt at grouping the inconsistencies into four categories:

1. Use of the same term for different disorders

Many authors use the term allergic or atopic conjunctivitis to name the overall range of ocular allergic disorders (9–14). But this is also one of the term used for the most frequently encountered subtype (7, 8, 14–20), the one also referred as to

hay fever, or seasonal and/or perennial conjunctivitis (see below).

2. Use of different terms for the same disorder

Use of different terms for the same disorder is also a frequent source of confusion. For example, vernal keratoconjunctivitis has been, and still is, also called spring catharr, vernal catharr or spring conjunctivitis (7, 10, 12, 21, 22). This creates confusion with the seasonal allergic conjunctivitis that a patient can manifest in the spring season. Vernal conjunctivitis (11, 13, 21, 23) and vernal disease (24) are other names less frequently used.

Another excellent example of this proliferation of different terms for the same disorder is the one first described as atopic keratoconjunctivitis by Hogan in 1952 (25), and subsequently ill-defined or referred to as chronic blepharoconjunctivitis associated with lid eczema (9, 10). This disorder is also known under several additional names: eczematous blepharitis, blepharoconjunctivitis or keratoconjunctivitis (12, 17, 26), atopic blepharoconjunctivitis (7, 27), atopic conjunctivitis (22), atopic dermatitis-associated conjunctivitis (15, 29) chronic allergic conjunctivitis (15, 29) or allergic keratoconjunctivitis (30). The most followed tendency at present however, is to keep the name given by Hogan (1, 5, 7, 11, 13, 14, 16, 18–20, 23, 29, 31–36).

In the past, many different names have been given to the most common form of ocular allergy. Perhaps the two most frequent terms in use are allergic conjunctivitis (7, 8, 14, 16–20) and atopic conjunctivitis (12, 15, 22). Most of the other designations for this disorder in fact represent different subtypes: seasonal and/or perennial conjunctivitis (2, 7, 14, 16, 18, 20, 28, 31, 33) and hay fever conjunctivitis (1, 13, 15–17, 22, 28). There seems to be a great deal of confusion about the most appropriate general term and the terms that should be reserved for the different subtypes of this disease.

3. Improper designation of disorders as allergic conditions

Some disorders are immune-mediated but by mechanisms in which allergy (defined as a type I hypersensitivity reaction) is not implicated. Much of the confusion comes from the different definitions of the term "allergy" throughout history. For many years, some authors have referred to the four types of hypersensitiv-

ity reactions described in 1963 by Gell and Coombs (37) as allergic reactions (10, 21, 26).

For instance, disorders such as marginal corneal infiltrates (also referred to as marginal keratitis) secondary to blepharitis have been included, mostly in the past, as an allergic disorder. As such, they have been called microbioallergic blepharitis, marginal allergic infiltrates or marginal allergic keratitis (9, 10, 12, 21). Likewise, superior limbic keratoconjunctivitis or keratitis and phlyctenular keratoconjunctivitis and some other immune-mediated (but not allergic) conditions were included in old reports as being allergic in nature (10, 21, 26).

Similarly, immune-mediated problems in contact lens wearers, and more often problems arising from non-immune mechanisms (e.g., irritation, intolerance, toxicity) are sometimes referred to as allergic problems related to contact lenses (38).

Perhaps the most frequent controversy at present is whether or not to consider contact dermatitis-blepharoconjunctivitis, (in other words, ocular involvement based on a type IV hypersensitivity mechanism) as a subtype of allergy (1, 9–12, 14, 20, 21, 24, 28, 39, 40). This will depend on the definition adopted under the term allergy, which is discussed below. The present tendency, however is to consider the ocular involvement due to delayed-type hypersensitivity as different from allergy (6).

4. General confusion regarding the definitions of allergy and atopy

To understand the source of this misunderstanding, one needs to know what allergologists mean by allergy and atopy. It seems that there is a notable disagreement among them about the meaning of these two terms (6, 40). For instance, some authors consider allergy to be any change in reactivity of the natural form of the host response. Others define allergy as an unexpected response to a foreign antigen that is not harmful to most people. The majority, however, describe allergy as a condition in which an IgE mechanism is somehow implicated in the etiopathogenesis of that particular disorder (6, 40). This confusion has an explanation going back into the history of Allergy (cited in Mygind et al. 1996) (40). Clemens von Pirquet and Bela Shick coined the word allergy in 1906 for the concept of changed reactivity (*allos* meaning different or changed, and *ergos* meaning work

or action). However, they could not define the mechanism behind the condition they had termed allergy. Interestingly, the condition first called "allergy" was, in fact, serum sickness. Later, in 1923, Coca and Cook defined as "atopy" the familial tendency to develop allergic diseases such as asthma and hay fever. It was later found out that this inherited predisposition could be transmitted by blood, through a factor that was called "reagin". It was not until 1968 that the Ishizaka team (husband and wife) and independently, Johansson and Bennich, isolated that reagin and identified it as an immunoglobulin which they called immunoglobulin E (IgE). Today, it is well established that IgE is the carrier of the biological features of the previously called reaginic antibodies and thus, of allergic phenomena (6, 40). Later, Gell and Coombs defined the four well known types of hypersensitivity. The terms allergic, anaphylactic and atopic were relegated to type I hypersensitivity reactions, exclusively (37).

The present tendency is to define allergy as processes mediated (at least partially) by a type I IgE-related hypersensitivity mechanism (including early and late phase responses). Atopy is usually considered the inherited or genetic predisposition to produce IgE (i.e., a familial tendency to suffer from allergic disorders). Despite these tendencies, different terminology is still found in general allergy references (6, 40). For instance, some consider allergy equal to hypersensitivity, and therefore immune-mediated is the same as allergy-mediated. Some authors believe that atopic and allergic are synonymous, while others disagree, stating that atopy could be allergic or non-allergic depending on whether an external antigen can be identified (40).

In summary, allergy seems to be restricted at present to those diseases in which, an IgE-dependent or related mechanism (i.e., type I) can be found in their etiopathogenesis (6). It should be further clarified that allergy is no longer restricted to IgE-mediated mast cell degranulation, but rather involves a much more complex phenomenon involving T cells and many other cells and molecules (6).

Classification of ocular atopic/allergic disorders

The following is a summary of the most recent tendency found in modern manuscripts and books.

Atopy, at present, tends to be defined by a constellation of findings occurring in persons with hereditary background of allergic disease. Atopic phenomena are entirely or partially responsible for several disorders of the ocular surface, and these would be the only ones that could be safely denominated as allergic ocular disorders. This implies that the concept of allergy would include disorders mediated, at least in some aspects, by an IgE-dependent (type I hypersensitivity) mechanism. It is therefore taken for granted that other mechanisms can also be involved, with a type IV hypersensitivity, or delayed T cell reaction, one of the most important.

Based on these assumptions, the following disorders can be considered allergic in nature, and subsequently, most of today's contemporary authors have classified them accordingly:

1. Allergic conjunctivitis (AC)
 - 1.1 Acute allergic conjunctivitis
 - 1.1.1. Seasonal or hay fever (induced by seasonal allergens)
 - 1.1.2. Toxic-induced (induced by acute contact with irritants, drugs, preservatives, etc)
 - 1.2 Chronic allergic conjunctivitis
 - 1.2.1. Perennial (induced by non-seasonal allergens)
 - 1.2.2. Toxic-induced (long-lasting form of 1.1.2.)
2. Giant papillary conjunctivitis (GPC)
3. Vernal keratoconjunctivitis (VKC)
 - 3.1 Palpebral
 - 3.2 Limbal
 - 3.3 Mixed
4. Atopic keratoconjunctivitis (AKC)

Allergic conjunctivitis is the most frequently encountered form of ocular allergy. By definition, it will never involve the cornea and therefore it is benign. Its acute form (acute allergic conjunctivitis) occurs when an antigen directly contacts the ocular surface. Conjunctival and lid edema and hyperemia develop rapidly and itching and tearing are the main symptoms (8, 18, 34).

When symptoms develop in certain seasons due to seasonal contact with environmental airborne antigens (allergens), the term acute seasonal allergic conjunctivitis seems to be the most suitable. Acute seasonal allergic conjunctivitis is synonymous with the ocular component of hay fever (rhinitis). In fact, acute seasonal allergic conjunctivitis will often be accompanied by rhinitis and even sinusitis. Seasonal allergic conjunc-

tivitis, probably one of the most common entities encountered in general ophthalmic practice, is therefore a recurrent disease associated with exposure to a variety of allergens and characterized by itching, burning, redness, chemosis, and lid edema. As said, these symptoms occur seasonally and disappear completely once the season is over, provided this is the only allergic disorder the patient has.

Chronic perennial allergic conjunctivitis is similar to seasonal allergic conjunctivitis, but without seasonal dependence. It is provoked by perennial allergens (e.g., house dust mites).

Acute allergic conjunctivitis may also be triggered by external non-airborne antigens such as drugs, contact lens solutions, irritants, and preservatives. Thus, this subtype of allergic conjunctivitis is called acute allergic toxic-induced conjunctivitis. This condition produces a similar symptomatology as previously described for seasonal conjunctivitis but with no seasonal component. If the offending product is identified and its use discontinued, the signs and symptoms will disappear. If the patient is unable or unwilling to avoid the offending product, the conjunctivitis will be long-lasting, and the proper term would be chronic allergic toxic-induced conjunctivitis. Although there is no sharp demarcation between acute and chronic inflammation, in practice, the clinical course of inflammation is termed acute if it last for hours, days or weeks and chronic if it last for months or years.

Use of the term "allergic conjunctivitis" to describe all ocular allergic disorders should be discouraged. Moreover, using the terms atopic conjunctivitis and allergic conjunctivitis as interchangeable synonyms should also be discouraged as it may lead to confusion with the disorder called atopic keratoconjunctivitis.

Allergic conjunctivitis is the only ocular phenomena that can be fully explained by a type I IgE-dependent mechanism (including late phase reactions). The remaining ocular allergic disorders have this mechanism implicated in their pathogenesis but not as the principal event. A cellular type IV reaction has been demonstrated in GPC, VKC and AKC in addition to many other factors, whose details are beyond the scope of this paper.

Giant papillary conjunctivitis (GPC) is an inflammatory reaction of the superior tarsal conjunctiva (manifesting giant papillae in late stages) that has been associ-

ated predominantly with contact lens wear. The condition is not limited to contact lens wearing patients, as a variety of foreign bodies on the external ocular surface can result in this condition. GPC does not normally involve the cornea. While many patients report a positive family history of atopy, it is not required for this condition which is limited to the eye (4, 34).

Vernal keratoconjunctivitis is a recurrent bilateral inflammation of the conjunctiva, more common in warm climates, and characterized by giant papillae of the superior tarsal conjunctiva, gelatinous hypertrophy of the limbus, and keratopathy. It is associated with intense itching, photophobia, and mucous discharge. As said for the previous disorder, this entity does not require a non-ocular allergic involvement (4, 34).

Atopic keratoconjunctivitis (AKC) includes multifactorial ocular surface disorders in a context of atopic dermatitis, either active or dormant. Symptoms include itching, burning, tearing, and an abundant mucous discharge. The disease may include lid eczema, chronic blepharitis, cicatrizing conjunctivitis and compromised vision from corneal scarring and neovascularization (5, 16, 34). AKC is the most severe and most difficult to manage ocular allergic disorder (16, 35, 36).

It is quite important not to omit the prefix "kerato" from the names for these two disorders (i.e., vernal and atopic keratoconjunctivitis). Both have the potential of involving the cornea and, subsequently compromising vision. In addition, this fact divides ocular atopic disorders into benign, non-sight-threatening (allergic conjunctivitis and giant papillary conjunctivitis), and those that are potentially severe or sight-threatening (vernal and atopic keratoconjunctivitis). Also of note is the particularly erroneous tendency found in many books, especially non-ophthalmic ones (6, 40), to consider ocular allergies as benign and always self-limiting disorders. This is linked to the tendency of non-ophthalmological sources to consider that "allergic conjunctivitis" or even worse, "hay fever", is the only allergic condition of the eyes (6, 40).

One may also wonder whether some of the names given to ocular allergic disorders are appropriate. However, this problem is so frequently encountered in medicine that many disease names would have to be removed or changed. In any

case, this could be a further matter of discussion and it is not the issue of this paper.

Lastly, although the conjunctiva is the most common target for allergic reactions, other disorders such as episcleritis and scleritis seem to be more frequently encountered in the context of atopy (34). Whether this is coincidental, given the high proportion of allergic persons, or whether a definite relationship exists deserves further consideration.

References

1. Abelson MB & Schaefer K (1993): Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. *Surv Ophthalmol* 38 (Suppl July-August): 115-132.
2. Foster CS (1994): Immunologic disorders of the conjunctiva, cornea, and sclera. In: Albert DM, Jakobiec FA (eds). *Principles and practice of ophthalmology*. Vol 1: 190-217. W.B. Saunders, Philadelphia.
3. Buckley RJ & Bacon AS (1996): Giant papillary conjunctivitis. In: Pepose JS, Holland GN, Wilhelmus KR (eds). *Ocular infection and immunity*: 359-366. Mosby, St. Louis.
4. Brody JM & Foster CS (1996): Vernal conjunctivitis. In: Pepose JS, Holland GN, Wilhelmus KR (eds). *Ocular infection and immunity*: 367-375. Mosby, St. Louis.
5. Liesegang TJ (1996): Atopic keratoconjunctivitis. In: Pepose JS, Holland GN, Wilhelmus KR (eds). *Ocular infection and immunity*: 376-390. Mosby, St. Louis.
6. Janeway CA, Travers P, Hunt S & Walport M (1997): *Immunobiology: the immune system in health and disease*. Current Biology Ltd, London.
7. McGill JJ, Holgate ST, Church MK, Anderson DF & Bacon A (1998): Allergic eye disease mechanisms. *Br J Ophthalmol* 82: 1203-1214.
8. Reiss J, Abelson MB, George MA & Wedner HJ (1996): Allergic conjunctivitis. In: Pepose JS, Holland GN, Wilhelmus KR (eds). *Ocular infection and immunity*: 345-358. Mosby, St. Louis.
9. Woods AC (1937): Clinical problem of allergy in relation to conjunctivitis and iritis. *Arch Ophthalmol* 17: 1-17.
10. Duke-Elder S (1965): Diseases of the outer eye. In: Duke-Elder S (ed). *System of Ophthalmology* vol III, part I: 432-496. Henry Kimpton, London.
11. Friedlaender MH (1985): Ocular allergy. *J Allergy Clin Immunol* 75: 645-657.
12. Dernouchamps JP, Hoebeke M & Michiels J (1987): Une classification des conjonctivites allergiques. *J Fr Ophtalmol* 10: 459-461.
13. Bonini St & Bonini S (1987): Studies of allergic conjunctivitis. *Chibret Intal J Ophthalmol* 5:12-22.
14. Friedlaender MH (1993): Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. *Surv Ophthalmol* 38 (Suppl July-August): 105-114.
15. Van Bijsterveld OP (1998): Allergic conjunctivitis. In: de Keizer RJW, Jager M, Kijlstra A (eds). *Handbook of Ocular Immunology*: 149-154. Aeolus Press, Buren.
16. Foster CS & Calonge M (1990): Atopic keratoconjunctivitis. *Ophthalmology* 97: 992-1000.
17. Collum LMT (1993): The management of ocular allergy. *Oc Immunol Inflamm* 1: 5-8.
18. Abelson MB, Udell IJ, Allansmith MR & Raizman MB (1994): Allergic and toxic reactions. In: Albert DM, Jakobiec FA (eds). *Principles and Practice of Ophthalmology*. Vol 1: 77-100. W.B. Saunders, Philadelphia.
19. Foster CS (1995): The pathophysiology of ocular allergy: current thinking. *Allergy* 50 (21 suppl): 6-9; discussion 34-38.
20. Donshik PC & Ehlers WH (1994): Clinical immunologic diseases. In: Smolin G, Thoft RA (eds). *The cornea, scientific foundations and clinical practice*. Little, Brown and Company, Boston.
21. Jones BR (1971): Allergic disease of the outer eye. *Trans Ophthalmol Soc UK* 91: 441-447.
22. Easty DL (1987): Allergy and the eye. In: Lee LTH, Kemeny DM (eds). *Allergy: An international textbook* 30: 513-530. John Wiley & Sons Ltd. QUITAR.
23. Allansmith MR (1982): The eye and immunology: 113-130. The C.V. Mosby Company, St. Louis.
24. Easty DL, Birkenshaw M, Merret T, Entwistle C & Amer B (1980): Immunological investigations in vernal eye disease. *Trans Ophthalmol Soc UK* 100: 98-107.
25. Hogan MJ (1952): Atopic keratoconjunctivitis. *Trans Am Ophthalmol Soc* 50: 265-281.
26. Friedlaender MH & Allansmith MR (1975): Ocular allergy. *Ann Ophthalmol* 7: 1171-1186.
27. Bacon et al, (1993): The origin of keratopathy in chronic allergic eye disease: a histopathological study. *Eye* 7 (Pt. 3 Suppl): 21-5.
28. BenEzra D (ed) (1994): Guidelines on the diagnosis and treatment of conjunctivitis. IV Non-infectious conjunctivitis. *Oc Immunol Inflamm* 2: S17-S23.
29. Tuft SJ, Ramakrishnan M, Seal DV, Kemeny DM & Buckley RJ (1992): Role of staphylococcus aureus in chronic allergic conjunctivitis. *Ophthalmology* 99: 180-184.
30. Dogru M, Katakami C, Nakagawa N, Tetsumoto K & Yamamoto M (1998): Impression cytology in atopic dermatitis. *Ophthalmology* 105: 1478-1484.
31. Allansmith MR & Ross RN (1986): Ocular allergy and mast cell stabilizers. *Surv Ophthalmol* 30: 229-244.
32. Buckley RJ (1988): Atopic disease of the cornea. In: Cavanagh HD (ed). *The cornea: transactions of the world congress on the cornea III*. Raven Press, New York.
33. Bloch-Michel E, Helleboid L & Le Corvec MP (1993): Chronic allergic conjunctivitis. *Oc Immunol Inflamm* 1: 9-12.
34. Foster CS & Sainz de la Maza M (1994): *The sclera*. Springer-Verlag, New York.
35. Hoang-Xuan T, Prisant O, Hannouche D & Robin H (1997): Systemic cyclosporine A in severe atopic keratoconjunctivitis. *Ophthalmology* 104: 1300-1305.
36. Hingorani M, Moodaley L, Calder VL, Buckley RJ & Lightman S (1998): A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. *Ophthalmology* 105: 1715-1720.
37. Gell PGH & Coombs RRA (1963): *Clinical aspects of immunology*: 317-337. Blackwell Scientific Publications.
38. Silbert JA (ed) (1994): *Anterior segment complications of contact lens wear*. Churchill Livingstone, New York.
39. Marsh RJ, Towns S & Evans KF (1978): Patch testing in ocular drug allergies. *Allergy* 98: 278-280.
40. Mygind N, Dahl R, Pedersen S & Thestrup-Pedersen K (1996): *Essential allergy*. Blackwell Science, Oxford.